

# Better Cancer-specific Survival in Younger Patients With Stage III Colorectal Cancer: A Propensity Score Matching Study From Japan

LIMING WANG, YASUMITSU HIRANO, GREGORY HENG, TOSHIMASA ISHII, HIROKA KONDO,  
KIYOKA HARA, NAO OBARA, MASAHIRO ASARI and SHIGEKI YAMAGUCHI

*Division of Gastroenterological Surgery, Saitama Medical University International Medical Center, Saitama, Japan*

**Abstract.** *Background/Aim:* The purpose of this study was to explore the perioperative, short-term, and long-term prognostic differences in colorectal cancer (CRC) between young and older patients. *Patients and Methods:* A total of 3095 patients were divided into young ( $\leq 45$  years;  $n=139$ ) and older ( $>45$  years;  $n=2956$ ) groups. Then, propensity score matching was performed for patients in stage I to III according to a ratio of 1:1. The clinicopathological factors and prognosis of the two groups were studied. *Results:* Young patients with CRC account for 4.49% of the total number of patients with CRC. Younger patients with CRC in stage I to III showed better cancer-specific survival (CSS). Older age was an independent risk factor for CSS prognosis. The CSS of the younger group was significantly better in stage I to III as a whole, but there was no difference in stage I and II subgroups – only in stage III. The proportion of young patients with stage III disease receiving first-line adjuvant chemotherapy was significantly higher. When young patients relapsed, they were more likely to receive second-line adjuvant chemotherapy or reoperation than older patients. *Conclusion:* Younger patients with stage III colorectal cancer had better CSS rates.

The incidence of colorectal cancer (CRC) in young patients is increasing in the United States (1). Despite advances in screening technology and treatment, CRC is the second leading cause of cancer-related deaths in Japan; more than 50,000 people died of CRC in 2016, many of whom were young patients (2).

*Correspondence to:* Liming Wang, MD, Ph.D., Division of Gastroenterological Surgery, Saitama Medical University International Medical Center, Hidaka, Saitama, Japan. Tel: +81 429844111, Fax: +81 429840054, e-mail: wuminami@hotmail.com

*Key Words:* Younger colorectal cancer, cancer-specific survival, propensity score matching.

CRC is relatively unique in that it affects a large age span, from young to old. There are few studies on young patients diagnosed with CRC and the clinical outcome of these patients is not clear. Previous reports have shown that younger patients with CRC are more likely to develop progressive disease and have a worse prognosis than older patients (3). However, other reports have suggested that young patients' survival rates are similar to those of older patients (4). The reason for this contradiction may be related to the individual study's definition of a "young" patient. Some studies classify any patients  $\leq 50$  years old (5, 6) as young, whereas other studies classify patients  $\leq 45$  years of age (7, 8) as young. In addition, the different clinical characteristics of the young and older patients may also lead to inconsistent results.

In recent years, propensity score matching (PSM) has been widely used in clinical studies to reduce differences between study groups (9, 10). The purpose of our study was to analyze, using PSM, the difference in prognosis between young and older patients with CRC during the perioperative, short-term, and long-term period.

## Patients and Methods

This was a 10-year retrospective cohort study of a high-volume cancer center in Japan. Cases were selected from 3570 patients with CRC who underwent surgical resection at the Saitama Medical University International Medical Center from October 2007 to December 2016. Patients with neuroendocrine colon tumors or without indications for surgery were excluded. All patients signed a written, informed consent form. The ethics committee of the Saitama Medical University International Medical Center approved the study.

The patients with CRC were divided into young ( $\leq 45$  years;  $n=139$ ) and old ( $>45$  years;  $n=2,956$ ) groups (Figure 1). The basic medical history and preoperative comorbidities of the patients were collected from the outpatient medical records, and short-term postoperative comorbidities were screened from the discharge summary. Resection specimens were classified pathologically according to the seventh edition of the International Union Against Cancer TNM classification. Propensity score weights were used to balance the basic variable logistic regression model using polynomials for comparative analysis.

Sex, family history, tumor location, postoperative complications, preoperative carcinoembryonic antigen (CEA) levels, surgical methods, tumor morphology, pathological type, peritoneal metastasis, depth of invasion, lymphatic infiltration, peripheral nerve invasion, blood vessel infiltration, and lymph node metastasis were included in the matching model. Independent risk factors for relapse-free survival (RFS) and cause-specific survival (CSS) were determined by Cox regression analysis and the Wald test.

All statistical analyses were performed using the SPSS software package version 22.0 for Macintosh (IBM Japan, Tokyo, Japan). Survival rates were drawn using the Kaplan-Meier method and log-rank test. A  $p$ -value  $<0.05$  was considered statistically significant.

## Results

A total of 3095 patients with primary CRC were included in this study, of which 2956 (95.51%) were  $>45$  years of age, and 139 patients (4.49%) were  $\leq 45$  years. First, the patients were analyzed by single factor analysis. There was a 20-year difference in the mean age of the 2 groups [mean (y)  $\pm$  SD,  $40 \pm 0.48$  vs.  $60 \pm 0.007$ ;  $p < 0.001$ ]. Compared to the older patients, the young CRC group had 1) more female patients (48.2% vs. 39.0%;  $p = 0.033$ ); 2) greater family history of CRC (29.5% vs. 18.4%;  $p = 0.002$ ); 3) more rectal cancer (54.0% vs. 39.8%;  $p = 0.001$ ); 4) a higher proportion of signet ring, mucinous, and low-differentiated adenocarcinoma (7.9% vs. 4.1%;  $p = 0.048$ ); 5) more protruding-proliferative type (36.7% vs. 25.2%;  $p = 0.004$ ); and 6) more shallow infiltration (T1: 29.5% vs. 19.1%;  $p = 0.017$ ) than the older CRC group. Shallow infiltration was more easily detected in the early stage (stage I: 35.3% vs. 25.9%;  $p = 0.044$ ). However, there were no significant differences in CEA  $\geq 5$  ng/ml (31.7% vs. 37.6%;  $p = 0.178$ ), peritoneal metastasis (43.2% vs. 40.8%;  $p = 0.597$ ), and lymphatic infiltration (37.4% vs. 31.6%;  $p = 0.162$ ). Regarding surgery type, there was no difference in whether the operation was open or laparoscopic between the 2 groups ( $p = 0.331$ ) (Table I).

Next, we performed multivariate analysis on the 2 groups before matching. It was found that patients with rectal cancer [hazard ratio (HR)=0.755; 95% confidence interval (CI)=0.613-0.931;  $p = 0.009$ ] and ulcerative and infiltrating proliferation (HR=0.495; 95%CI=0.34-0.720;  $p < 0.001$ ) were more prone to relapse than those with colon cancer. Patients with pathology revealing signet ring cell carcinoma, mucinous adenocarcinoma, and poorly differentiated adenocarcinoma were more likely to relapse than those with adenocarcinoma (HR=0.592; 95%CI=0.395-0.888;  $p = 0.011$ ).

In the group with CEA level  $\geq 5$  ng/ml, recurrence rates increased (HR=0.548; 95%CI=0.443-0.676;  $p < 0.001$ ), and CSS decreased significantly (HR=0.596; 95%CI=0.459-0.774;  $p < 0.001$ ). Lymphatic invasion, vascular invasion, and lymph node metastasis were also independent risk factors for both RFS and CSS: 1) lymphatic invasion for RFS (HR=0.706; 95%CI=0.564-0.883;  $p = 0.002$ ) and CSS

(HR=0.639; 95%CI=0.485-0.841;  $p = 0.001$ ); 2) vascular invasion for RFS (HR=0.554; 95%CI=0.423-0.725;  $p < 0.001$ ) and CSS (HR=0.529; 95%CI=0.386-0.726;  $p < 0.001$ ); and 3) lymph node metastasis for RFS (HR=0.376; 95%CI=0.264-.536;  $p < 0.001$ ) and for CSS (HR=0.559; 95%CI=0.339-0.923;  $p = 0.023$ ) (Table III).

We then matched the 2 groups with a propensity score of 1:1. A total of 139 young patients were compared with 139 older patients. Initially, we matched all cases of stage I to IV and found no differences in CSS between the 2 groups, as well as in stage IV (before PSM,  $p = 0.392$ ; after PSM,  $p = 0.257$ ).

Then we matched 114 patients in stage I to III again, with a mean age difference of about 27 years ( $40 \pm 0.48$  vs.  $67 \pm 0.54$ ;  $p < 0.001$ ). There was no statistical difference in patient clinical characteristics between the 2 groups, including the number of lymph nodes removed (Table II).

We analyzed the prognosis of patients before PSM. There was no difference in overall CSS and RFS rate. The younger patients with CRC had a better CSS rate for stage I to III, and after matching, the difference became more obvious (before PSM,  $p = 0.046$ ; after PSM,  $p = 0.005$ ) (Figure 2A and 3A). There was no difference between the younger and older patients with CRC in stage II (before PSM,  $p = 0.410$ ; after PSM,  $p = 0.983$ ) (Figure 2B and 3B). There was no difference in RFS among the various stages. Interestingly, there was no significant difference between the 2 groups in the prematching stage III, but after matching, the CSS prognosis in the older group was significantly worse (before PSM,  $p = 0.405$ ; in PSM,  $p = 0.031$ ) (Figure 2C and 3C).

Cox regression analysis after matching showed that the older group (HR=0.247; 95%CI=0.085-0.719;  $p = 0.010$ ) and higher CEA level were independent risk factors (HR=0.108; 95%CI=0.027-0.430;  $p = 0.002$ ) for CSS (Table IV).

Considering that the patient's underlying disease and postoperative recovery may affect the prognosis, we compared the perioperative factors between the 2 groups. As expected, the background of the patients after matching showed that the older group had more diabetes mellitus (14.9% vs. 1.8%;  $p < 0.001$ ) and hypertension diagnoses (43.8% vs 6.1%;  $p < 0.001$ ) and preoperative surgical history (28.9% vs. 12.2%;  $p < 0.001$ ). However, there was no significant difference in operation time, blood loss, postoperative food intake, hospital stay, length of specimen resection, postoperative complications (*e.g.*, anastomotic leakage) and recurrence (Table IV). We further investigated the postoperative adjuvant chemotherapy in patients with stage III, and we found that the proportion receiving adjuvant chemotherapy in the younger group was much higher (76.9% vs. 38.5%;  $p < 0.001$ ). The proportion of the 2 groups receiving second-line chemotherapy or reoperation after relapse was significantly higher in the younger group than in the older group (81.8% vs. 40%;  $p < 0.001$ ) (Table V). Eleven patients (28.2%) in the young group relapsed, 6 patients (54.5%) had additional targeted drug chemotherapy, and 3

Table I. Clinicopathological parameters for patients before matching.

Parameters	Younger CRC	Older CRC	p-Value
Gender (Total n=)	139	2956	
Male	72 (51.8%)	1.802 (62.0%)	
Female	67 (48.2%)	1.154 (39.0%)	0.033
Age (year)	40±0.48	60±0.007	<0.001
Family CRC history			
No	98 (70.5%)	2.413 (81.6%)	
Yes	41 (29.5%)	543 (18.4%)	0.002
Tumor location			
Colon	64 (46.0%)	1777 (60.2%)	
Rectum	75 (54.0%)	1179 (39.8%)	0.001
CEA (ng/ml)			
<5	95 (68.3%)	1.844 (62.4%)	
≥5	44 (31.7%)	1.112 (37.6%)	0.178
Approach of operation			
Open	23 (16.5%)	604 (20.4%)	
Laparoscopic	116 (83.5%)	2.352 (79.6%)	0.331
Gross type			
Protruding	51 (36.7%)	745 (25.2%)	
Ulcerative & infiltrative	88 (63.3%)	2211 (74.8%)	0.004
Histopathology			
Adenocarcinoma	128 (92.1%)	2835 (95.9%)	
Mucinous, signet, poor	11 (7.9%)	121 (4.1%)	0.048
Perineural invasion			
No	79 (56.8%)	1.749 (59.2%)	
Yes	60 (43.2%)	1.207 (40.8%)	0.597
Infiltration lymphatic vessels			
No	87 (62.6%)	2.023 (68.4%)	
Yes	52 (37.4%)	933 (31.6%)	0.162
Vascular invasion			
No	60 (43.2%)	1.184 (40.1%)	
Yes	79 (56.8%)	1.772 (59.9%)	0.48
Infiltration type			
Inflated	36 (25.9%)	452 (15.3%)	
Infiltrating	103 (74.1%)	2.504 (84.7%)	0.002
Infiltration depth			
T1	41 (29.5%)	564 (19.1%)	
T2	18 (12.9%)	397 (13.4%)	
T3	62 (44.6%)	1.633 (55.2%)	
T4	18 (12.9%)	362 (12.2%)	0.017
Stage			
I	49 (35.3%)	767 (25.9%)	
II	28 (20.1%)	843 (28.5%)	
III	40 (28.8%)	924 (31.3%)	
IV	22 (15.8%)	422 (14.3%)	0.044

patients (27.3%) had reoperation performed. However, in the older group, 15 (38.5%) patients relapsed, 8 patients (53.3%) chose hospice, 5 (33.3%) received second-line chemotherapy, and just 1 (6.7%) patient elected to have surgery.

## Discussion

Current European guidelines recommend CRC screening from the age of 50. In 2018, the American Cancer Society

Table II. Clinicopathological parameters for patients in stage I-III after matching.

Parameters	Younger CRC	Older CRC	p-Value
Gender (Total n=)	114	114	
Male	59 (51.8%)	59 (51.8%)	
Female	55 (48.2%)	55 (48.2%)	1
Age (year)	40±0.48	67±0.54	<0.001
Family CRC history			
No	79 (69.3%)	87 (76.3%)	
Yes	35 (30.7%)	27 (23.7%)	0.297
Tumor location			
Colon	48 (42.1%)	50 (43.9%)	
Rectum	66 (57.9%)	64 (56.1%)	0.894
Postoperative complications			
No	84 (73.7%)	91 (79.8%)	
Yes	30 (26.3%)	23 (20.2%)	0.347
CEA (ng/ml)			
<5	81 (71.1%)	82 (71.9%)	
≥5	33 (28.9%)	32 (28.1%)	1
Approach of operation			
Open	14 (12.3%)	13 (11.4%)	
Laparoscopic	100 (87.7%)	101 (88.6%)	1
Gross type			
Protruding	46 (40.4%)	48 (42.1%)	
Ulcerative & infiltrative	68 (59.6%)	66 (58.8%)	0.893
Histopathology			
Adenocarcinoma	106 (93.0%)	110 (96.5%)	
Mucinous, signet, poor	8 (7.0%)	4 (3.5%)	0.375
Perineural invasion			
No	73 (64.0%)	75 (65.8%)	
Yes	41 (36.0%)	39 (34.2%)	0.89
Infiltration lymphatic vessels			
No	79 (69.3%)	75 (65.8%)	
Yes	35 (30.7%)	39 (34.2%)	0.671
Vascular invasion			
No	54 (47.4%)	50 (43.9%)	
Yes	60 (52.6%)	64 (56.1%)	0.69
Infiltration type			
Inflated	34 (29.8%)	30 (26.3%)	
Infiltrating	189 (70.2%)	84 (73.7%)	0.659
Infiltration depth			
T1	39 (29.5%)	39 (29.5%)	
T2	18 (12.9%)	18 (12.9%)	
T3	51 (44.6%)	51 (44.6%)	
T4	6 (12.9%)	6 (12.9%)	1
Stage			
I	48 (42.1%)	48 (42.1%)	
II	27 (23.7%)	27 (23.7%)	
III	39 (34.2%)	39 (34.2%)	1
Lymph node resections (n=)	31.6±1.7	30.7±1.2	0.118

recommended screening from the age of 45 (11). This study is based on the new American colorectal screening guidelines. Patients under the age of 45 were defined as the young group. The average age of patients in the young group was 40 years old, and their family history of CRC was close to 30%, which is

Table III. Cox regression model comparing the prognosis of patients in stage I-III before matching.

Variable	Relapse-free survival			Cancer specific survival		
	HR	95%CI	p-Value	HR	95%CI	p-Value
Older vs. Younger	1.032	0.63-1.689	0.901	2.303	0.945-5.61	0.066
Female vs. Male	1.11	0.894-1.378	0.346	1.434	1.092-1.883	0.01
Family CRC history, yes vs. no	1.037	0.825-1.394	0.599	0.837	0.591-1.185	0.315
Rectum vs. Colon	0.755	0.613-0.931	0.009	1.165	0.9-1.508	0.247
CEA level (≥5 ng/ml), yes vs. no	0.548	0.443-0.676	0	0.596	0.459-0.774	0
Gross type, Ulcerative and Infiltrative vs. Protruding	0.495	0.34-0.720	0	1.169	0.832-1.642	0.369
MUC, SRC, Poor vs. ADC	0.592	0.395-0.888	0.011	0.648	0.382-1.099	0.108
Perineural invasion, yes vs. no	0.982	0.704-1.368	0.913	1.154	0.707-1.884	0.568
Lymphatic invasion, yes vs. no	0.706	0.564-0.883	0.002	0.639	0.485-0.841	0.001
Vascular invasion, yes vs. no	0.554	0.423-0.725	0	0.529	0.386-0.726	0
INF b,c vs. INFa	0.743	0.479-1.153	0.185	0.892	0.58-1.374	0.605
Lymph node metastasis, yes vs. no	0.376	0.264-0.536	0	0.559	0.339-0.923	0.023

Table IV. Cox regression model comparing the prognosis of patient in stage I-III after matching.

Variable	Relapse-free survival			Cancer specific survival		
	HR	95%CI	p-Value	HR	95%CI	p-Value
Older vs. Younger	0.908	0.443-1.859	0.792	0.247	0.085-0.719	0.01
Female vs. Male	1.191	0.580-2.445	0.635	0.908	0.363-2.270	0.837
Rectum vs. Colon	0.774	0.357-1.677	0.516	1.876	0.737- 4.77	0.187
CEA level (≥5 ng/ml), yes vs. no	0.477	0.210-1.085	0.077	0.108	0.027-0.430	0.002
Gross type, Ulcerative and Infiltrative vs. Protruding	0.507	0.140-1.841	0.302	4.081	0.697-23.91	0.119
MUC, SRC, Poor vs. ADC	1.361	0.376-4.927	0.639	0.896	0.182-4.418	0.893
Perineural invasion, yes vs. no	0.423	0.084-2.130	0.297	0.741	0.045-12.19	0.834
Lymphatic invasion, yes vs. no	1.407	0.636-3.112	0.4	0.705	0.255-1.948	0.501
Vascular invasion, yes vs. no	0.581	0.228-1.480	0.255	0.408	0.109-1.52	0.182
INF b,c vs. INFa	1.591	0.526-4.810	0.411	1.741	0.364-8.326	0.487
Lymph node metastasis, yes vs. no	0.209	0.055-1.525	0.144	0.343	0.019-6.160	0.468

ADC: Adenocarcinoma; CEA: carcinoembryonic antigen; CI: confidence interval; CRC: colorectal cancer; HR: hazard ratio; Muc: mucinous adenocarcinoma; Poor: poor poorly differentiated adenocarcinoma; SRC: signet ring cell carcinoma; INF: infiltrating pattern of invasion; INFa: swelling proliferation; INF c: invasive proliferation; INF b: between a and c; vs., versus.

much higher than that of the older group. Therefore, this reinforces the need to screen for a family history of CRC in patients from 40 years of age. Unlike previous reports (12), our study found that compared with older patients, invasive proliferative CRC in young patients was less common, and the number of patients in stage T1 was relatively high. This may explain why our findings indicated that the CSS prognosis was better in the young group in stage I to III. Contrary to some reports, we did not find any statistically significant differences in DFS before or after the match between the 2 groups (12, 13). This is also possibly due to the fact that 35.3% of the young patients were in stage I, which is 10% more than the older group, or may also be related to stable postoperative performance.

In Cox regression analysis, vascular infiltration and lymphatic invasion are considered to be independent risk

factors for RFS and CSS. However, in this study, we did not find any difference between the 2 groups for RFS and CSS. There are reports in the literature that the number of lymph nodes removed is related to the prognosis of tumor treatment (14, 15). Considering that lymph node metastasis was a common independent risk factor for RFS and CSS before matching, we aimed to keep the number of resected lymph nodes similar when performing PSM. In Japan, surgeons generally dissect the lymph nodes after surgery instead of handing the specimens to the pathologist. This makes it easier to collect smaller lymph nodes while the specimens are still fresh. The number of harvested lymph nodes is approximately 30, which is more conducive to lymph node analysis.

In the matched Cox regression analysis, we surprisingly found that older age was an independent high risk factor for

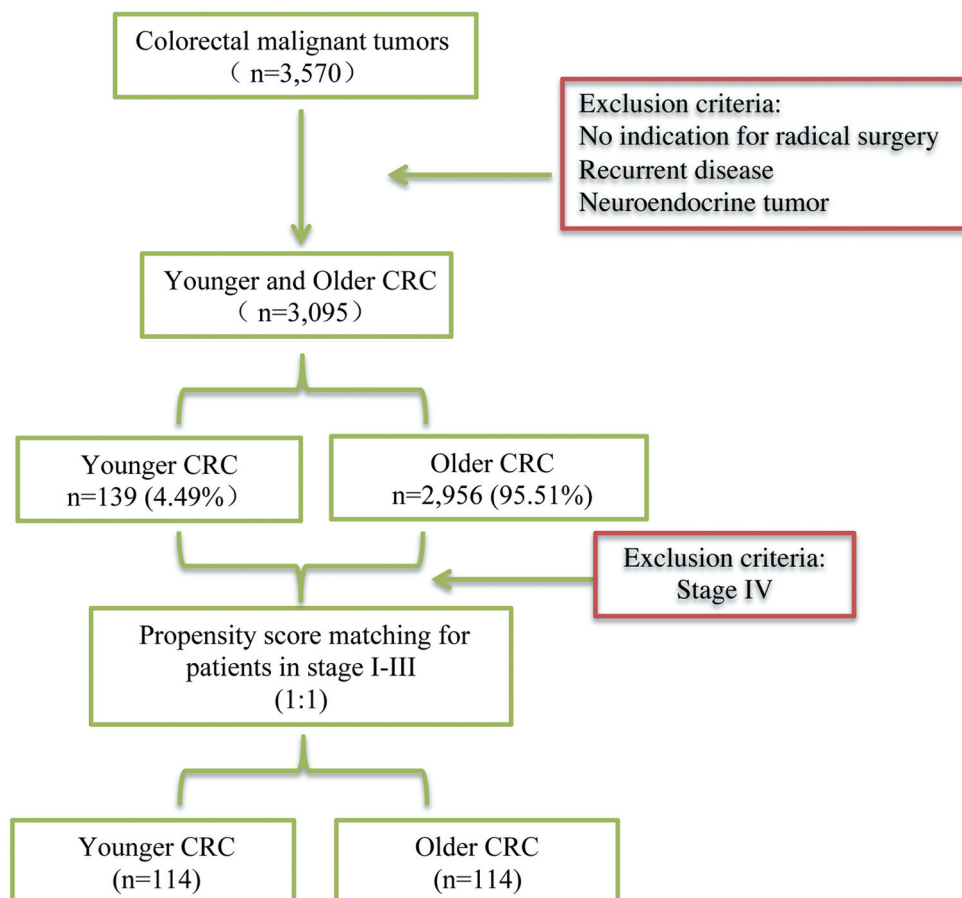


Figure 1. Research flow chart. CRC: Colorectal cancer.

CSS. This is also one of the interesting findings of our study which indicates that, when keeping all patient variables constant, older patients were more likely to have a worse prognosis. This finding coincides with previous reports (5, 16).

Surgical treatment is a vital part of colorectal treatment. In our study, there were no differences in postoperative results between the 2 groups due to age differences. We found that patients in stage I and II can have better CSS after rigorous surgical resection. In other words, regardless of age, early screening is extremely important. Only in stage III we found that when the number of lymph nodes cleared was equal, CSS in the young group was far better than that in the older group. This highlights the fact that, although the young group of patients had an earlier onset, the prognosis may not be necessarily poor. In addition to the homogeneous perioperative performance, we found that for patients in stage III, the proportion of postoperative adjuvant chemotherapy may directly affect the long-term survival rate of patients. We found that 53.3% of young patients chose oxaliplatin-containing chemotherapy after central vein chemotherapy pump implantation. In contrast, 66.7% of older

patients were more inclined to take orally chemotherapy drugs. Discovering how to improve the adjuvant chemotherapy introduction rate in older patients will be critical for improving the clinical outcome of CRC in that population. Young patients were more tolerant of second-line chemotherapy or reoperation in this research, which may also be one of the reasons for the difference in prognosis between the 2 groups.

This study does have some limitations. Some studies have reported that there are differences in microsatellite instability and *KRAS* and *BRAF* gene variations in young and older patients with CRC (4, 5, 17), which can also guide future clinical targeted therapy and immunotherapy. Secondly, although PSM reduced the differences between groups, it also greatly reduced the sample size, and it was impossible to completely match the preoperative comorbidities, which may also have caused some statistical bias. Further, despite follow-up results from high volume cancer centers over the past decade, the number of young patients was still small, so we hope that additional multi-center international research on young patients with CRC will be conducted in the future.

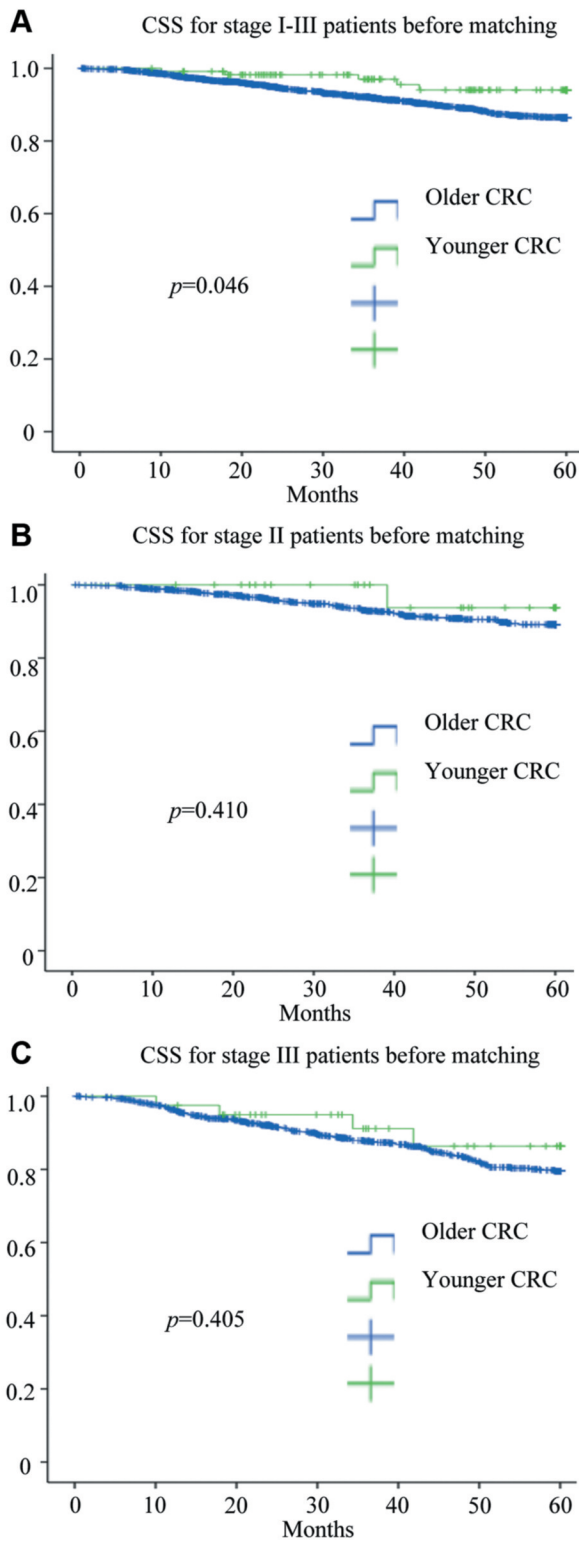


Figure 2. Cancer-specific survival rate before matching. A. Cancer-specific survival rate for patients in stage I to III before matching. B. Cancer-specific survival rate for patients in stage II patients before matching. C. Cancer-specific survival rate for patients in stage III patients before matching.

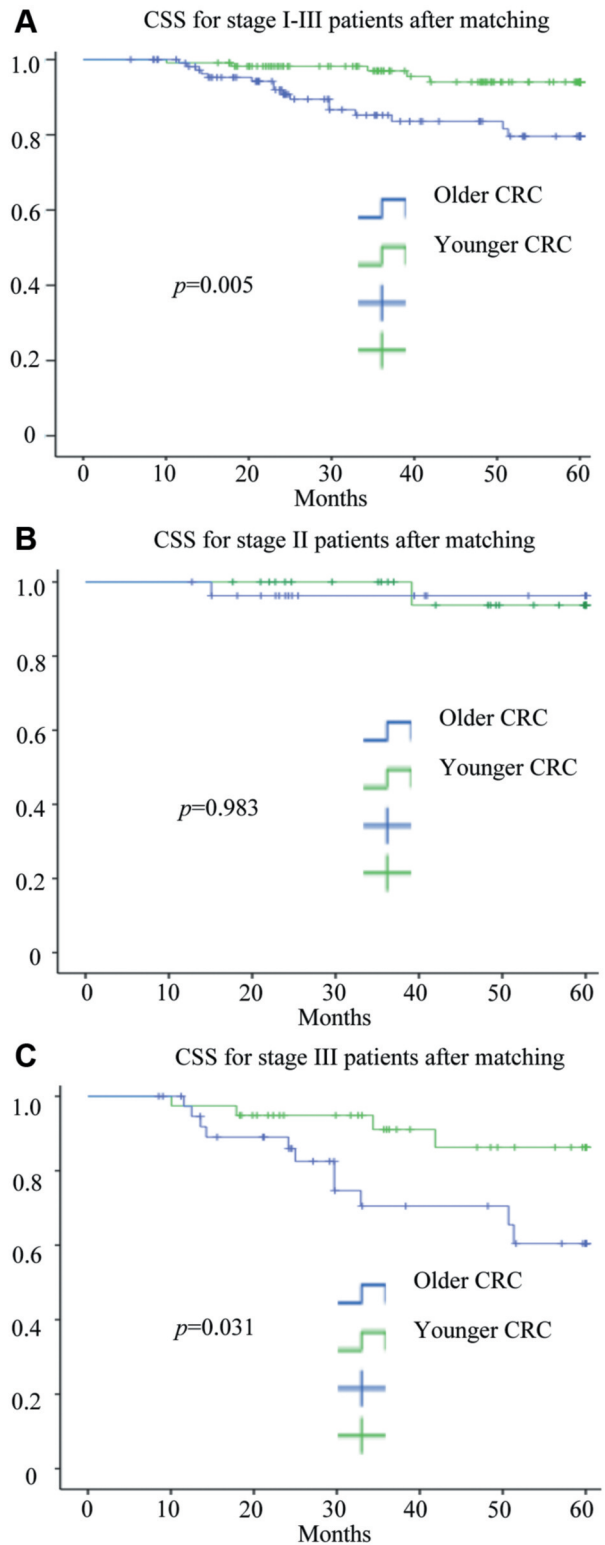


Figure 3. Cancer-specific survival rate after matching. A. Cancer-specific survival rate for patients in stage I-III patients after matching. B. Cancer-specific survival rate for patients in stage II patients after matching. C. Cancer-specific survival rate for patients in stage III patients after matching.

Table V. Characters of patients after matching.

Parameter	Younger (n=114)	Older (n=114)	p-Value
Diabetes	2 (1.8%)	17 (14.9%)	<0.001
Hypertension	7 (6.1%)	50 (43.8%)	<0.001
Abdominal surgery	14 (12.2%)	33 (28.9%)	<0.001
Respiratory diseases	4 (3.5%)	5 (4.4%)	N.S.
Intestinal obstruction	2 (1.8%)	2 (1.8%)	N.S.
Cerebrovascular disease	2 (1.8%)	4 (3.6%)	N.S.
Mental disorder	3 (2.6%)	4 (3.6%)	N.S.
Nephropathy	1 (0.9%)	2 (1.8%)	N.S.
Gynecology surgery	12 (10.5%)	13 (11.4%)	N.S.
Others	2 (1.8%)	4 (3.6%)	N.S.
Operative time, min	220.2±7.8	213.5±4.8	N.S.
Operative blood loss, ml	88.2±18.1	80.1±13.1	N.S.
Food intake, POD			
Median	3.0 (2-48)	3.0 (2-20)	
Mean	3.7±0.3	3.3±0.1	N.S.
Discharge, POD			
Median	7.0 (4-78)	7.0 (5-57)	
Mean	10.3±0.8	9.6±0.4	N.S.
Resection margin, cm			
Proximal	13.1±1.1	12.7±0.4	
Distal	5.9±0.4	6.8±0.3	N.S.
Lymph node dissection			
D3/D2/D1	90/19/5	88/20/6	N.S.
Anastomotic leakage	6 (5.2%)	7 (6.1%)	N.S.
Bowel obstruction	9 (7.8%)	8 (7.0%)	N.S.
Wound infection	2 (1.8%)	3 (2.6%)	N.S.
Bleeding	6 (5.2%)	2 (1.8%)	N.S.
Pneumonia	0 (0.0%)	2 (1.8%)	N.S.
Dehydration from diarrhea	2 (1.8%)	1 (0.9%)	N.S.
Recurrence	17 (14.92%)	16 (14.0%)	N.S.
Adjuvant chemotherapy for patients in Stage III	30/39 (76.9%)	15/39 (38.5%)	<0.001
Chemotherapy and reoperation after relapse in stage III	9/11 (81.8%)	6/15 (40%)	0.048

D3: Dissection of the third group (central) lymph nodes; D2: dissection of the second group (middle) lymph nodes; D1: dissection of the first group (marginal intestine) lymph nodes; POD, post-operation days.

In summary, this study found that age higher than 45 years was an independent risk factor for CRC, and young patients with stage III CRC have better CSS. Young patients have higher compliance with postoperative adjuvant chemotherapy and have a better chance of having second-line adjuvant chemotherapy or reoperation when they relapse.

## Conclusion

Younger patients with stage III CRC have better CSS rates, and improving postoperative adjuvant chemotherapy compliance may be a critical area to target for improving outcomes.

## Conflicts of Interest

The Authors have no competing interests to declare with respect to this study.

## Authors' Contributions

LMW drafted the manuscript. YH, GH, TI, HK, KH, NO, MA and SY reviewed its content. All authors have read and approved the final submission.

## Acknowledgements

Thanks are extended to BioMed Proofreading LLC for English copyediting.

## References

- Bailey CE, Hu CY, You YN, Bednarski BK, Rodriguez-Bigas MA, Skibber JM, Cantor SB and Chang GJ: Increasing disparities in the age-related incidences of colon and rectal cancers in the united states, 1975-2010. *JAMA Surg* 150(1): 17-22, 2015. PMID: 25372703. DOI: 10.1001/jamasurg.2014.1756

- 2 Hashiguchi Y, Muro K, Saito Y, Ito Y, Ajioka Y, Hamaguchi T, Hasegawa K, Hotta K, Ishida H, Ishiguro M, Ishihara S, Kanemitsu Y, Kinugasa Y, Murofushi K, Nakajima TE, Oka S, Tanaka T, Taniguchi H, Tsuji A, Uehara K, Ueno H, Yamanaka T, Yamazaki K, Yoshida M, Yoshino T, Itabashi M, Sakamaki K, Sano K, Shimada Y, Tanaka S, Uetake H, Yamaguchi S, Yamaguchi N, Kobayashi H, Matsuda K, Kotake K, Sugihara K, Japanese Society for Cancer of the C and Rectum: Japanese society for cancer of the colon and rectum (jscr) guidelines 2019 for the treatment of colorectal cancer. *Int J Clin Oncol* 25(1): 1-42, 2020. PMID: 31203527. DOI: 10.1007/s10147-019-01485-z
- 3 Shida D, Ahiko Y, Tanabe T, Yoshida T, Tsukamoto S, Ochiai H, Takashima A, Boku N and Kanemitsu Y: Shorter survival in adolescent and young adult patients, compared to adult patients, with stage iv colorectal cancer in japan. *BMC Cancer* 18(1): 334, 2018. PMID: 29587683. DOI: 10.1186/s12885-018-4241-9
- 4 Perrott S, Laurie K, Laws K, Johnes A, Miedzybrodzka Z and Samuel L: Young-onset colorectal cancer in the north east of scotland: Survival, clinico-pathological features and genetics. *BMC Cancer* 20(1): 108, 2020. PMID: 32041565. DOI: 10.1186/s12885-020-6606-0
- 5 Willauer AN, Liu Y, Pereira AAL, Lam M, Morris JS, Raghav KPS, Morris VK, Menter D, Broaddus R, Meric-Bernstam F, Hayes-Jordan A, Huh W, Overman MJ, Kopetz S and Loree JM: Clinical and molecular characterization of early-onset colorectal cancer. *Cancer* 125(12): 2002-2010, 2019. PMID: 30854646. DOI: 10.1002/cncr.31994
- 6 Rex DK, Boland CR, Dominitz JA, Giardiello FM, Johnson DA, Kaltenbach T, Levin TR, Lieberman D and Robertson DJ: Colorectal cancer screening: Recommendations for physicians and patients from the u.s. Multi-society task force on colorectal cancer. *Gastrointest Endosc* 86(1): 18-33, 2017. PMID: 28600070. DOI: 10.1016/j.gie.2017.04.003
- 7 Saraste D, Jaras J and Martling A: Population-based analysis of outcomes with early-age colorectal cancer. *Br J Surg* 107(3): 301-309, 2020. PMID: 31925793. DOI: 10.1002/bjbs.11333
- 8 Wolf AMD, Fonham ETH, Church TR, Flowers CR, Guerra CE, LaMonte SJ, Etzioni R, McKenna MT, Oeffinger KC, Shih YT, Walter LC, Andrews KS, Brawley OW, Brooks D, Fedewa SA, Manassaram-Baptiste D, Siegel RL, Wender RC and Smith RA: Colorectal cancer screening for average-risk adults: 2018 guideline update from the american cancer society. *CA Cancer J Clin* 68(4): 250-281, 2018. PMID: 29846947. DOI: 10.3322/caac.21457
- 9 Hirano Y, Hiranuma C, Hattori M, Douden K and Yamaguchi S: Single-port laparoscopic colectomy in elderly patients with colon cancer: A propensity score-matched comparison with younger patients. *Asian J Endosc Surg*, 2019. PMID: 31250557. DOI: 10.1111/ases.12719
- 10 Kanda M, Oba K, Aoyama T, Kashiwabara K, Mayanagi S, Maeda H, Honda M, Hamada C, Sadahiro S, Sakamoto J, Saji S, Yoshikawa T and Japanese Foundation for Multidisciplinary Treatment of C: Clinical signatures of mucinous and poorly differentiated subtypes of colorectal adenocarcinomas by a propensity score analysis of an independent patient database from three phase III trials. *Dis Colon Rectum* 61(4): 461-471, 2018. PMID: 29521828. DOI: 10.1097/DCR.0000000000001022
- 11 Vuik FE, Nieuwenburg SA, Bardou M, Lansdorp-Vogelaar I, Dinis-Ribeiro M, Bento MJ, Zadnik V, Pellise M, Esteban L, Kaminski MF, Suchanek S, Ngo O, Majek O, Leja M, Kuipers EJ and Spaander MC: Increasing incidence of colorectal cancer in young adults in europe over the last 25 years. *Gut* 68(10): 1820-1826, 2019. PMID: 31097539. DOI: 10.1136/gutjnl-2018-317592
- 12 Taggarshie D, Rehil N, Sharma S, Flynn JC and Damadi A: Colorectal cancer: Are the "young" being overlooked? *Am J Surg* 205(3): 312-316; discussion 316, 2013. PMID: 23414955. DOI: 10.1016/j.amjsurg.2012.10.016
- 13 Segev L, Kalady MF, Plesec T, Mor E, Schtrechman G, Nissan A and Church JM: The location of premalignant colorectal polyps under age 50: A further rationale for screening sigmoidoscopy. *Int J Colorectal Dis* 35(3): 529-535, 2020. PMID: 31930456. DOI: 10.1007/s00384-020-03504-2
- 14 Le Voyer TE, Sigurdson ER, Hanlon AL, Mayer RJ, Macdonald JS, Catalano PJ and Haller DG: Colon cancer survival is associated with increasing number of lymph nodes analyzed: A secondary survey of intergroup trial int-0089. *J Clin Oncol* 21(15): 2912-2919, 2003. PMID: 12885809. DOI: 10.1200/JCO.2003.05.062
- 15 Chen SL and Bilchik AJ: More extensive nodal dissection improves survival for stages i to III of colon cancer: A population-based study. *Ann Surg* 244(4): 602-610, 2006. PMID: 16998369. DOI: 10.1097/01.sla.0000237655.11717.50
- 16 O'Connell JB, Maggard MA, Liu JH, Etzioni DA, Livingston EH and Ko CY: Do young colon cancer patients have worse outcomes? *World J Surg* 28(6): 558-562, 2004. DOI: 10.1007/s00268-004-7306-7
- 17 Tezcan G, Tunca B, Ak S, Cecener G and Egeli U: Molecular approach to genetic and epigenetic pathogenesis of early-onset colorectal cancer. *World J Gastrointest Oncol* 8(1): 83-98, 2016. PMID: 26798439. DOI: 10.4251/wjgo.v8.i1.83

Received June 3, 2020

Revised June 22, 2020

Accepted June 23, 2020